FORM PTO-1390 (Modified) (REV 11-98) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371	ATTORNEY'S DOCKET NUMBER BMID9817US U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR 09/806115

INTERNATIONAL APPLICATION NO. PCT/EP99/07222	INTERNATIONAL FILING DATE (29.09.99) 29 September 1999	PRIORITY DATE CLAIMED (29.09.98) 29 September 1998

TITLE OF INVENTION
METHOD FOR THE PHOTOMETRIC ANALYSIS OF TEST ELEMENTS

APPLICANT(S) FOR DO/EO/US
MILTNER, Karl; RUPPENDER, Uwe; WERSIG, Christian; and ZIMMER, Volker

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.

2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.

3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).

4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.

5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))

     a. ☒ is transmitted herewith (required only if not transmitted by the International Bureau).

     b. ☐ has been transmitted by the International Bureau.

     c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).

6. ☒ A translation of the International Application into English (35 U.S.C. 371(c)(2)).

7. ☒ A copy of the International Search Report (PCT/ISA/210).

8. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))

     a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).

     b. ☐ have been transmitted by the International Bureau.

     c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.

     d. ☐ have not been made and will not be made.

9. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).

10. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).

11. ☒ A copy of the International Preliminary Examination Report (PCT/IPEA/409).

12. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).

Items 13 to 20 below concern document(s) or information included:

13. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98

14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.

15. ☒ A **FIRST** preliminary amendment.

16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.

17. ☐ A substitute specification.

18. ☐ A change of power of attorney and/or address letter.

19. ☒ Certificate of Mailing by Express Mail

20. ☒ Other items or information:

     General Appointment of Representative for U.S. Patent and Trademark Office Matters; and
     Return postcard.

PCTUS1/REV03

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR 09/806115	INTERNATIONAL APPLICATION NO PCT/EP99/07222	ATTORNEY'S DOCKET NUMBER BMID9817US

21.   The following fees are submitted:.

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :

☐ Neither international preliminary examination (37 CFR 1.482) nor
 international search fee (37 CFR 1.445(a)(2) paid to USPTO
 and International Search Report not prepared by the EPO or JPO $970.00

☒ International preliminary examination fee (37 CFR 1.482) not paid to
 USPTO but Internation Search Report prepared by the EPO or JPO $840.00

☐ International preliminary examination fee (37 CFR 1.482) not paid to USPTO
 but international search fee (37 CFR 1.445(a)(2)) paid to USPTO $690.00

☐ International preliminary examination fee paid to USPTO (37 CFR 1.482)
 but all claims did not satisfy provisions of PCT Article 33(1)-(4) $670.00

☐ International preliminary examination fee paid to USPTO (37 CFR 1.482)
 and all claims satisfied provisions of PCT Article 33(1)-(4) $96.00

	CALCULATIONS PTO USE ONLY

ENTER APPROPRIATE BASIC FEE AMOUNT = $860.00

Surcharge of **$130.00** for furnishing the oath or declaration later than   ☐ 20   ☐ 30
months from the earliest claimed priority date (37 CFR 1.492 (e)). $0.00

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	- 20 =	0	x $18.00	$0.00	
Independent claims	- 3 =	0	x $78.00	$0.00	
Multiple Dependent Claims (check if applicable).			☐	$0.00	

TOTAL OF ABOVE CALCULATIONS = $860.00

Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity Statement
must also be filed (Note 37 CFR 1.9, 1.27, 1.28) **(check if applicable).**   ☐ $0.00

SUBTOTAL = $860.00

Processing fee of **$130.00** for furnishing the English translation later than   ☐ 20   ☐ 30
months from the earliest claimed priority date (37 CFR 1.492 (f)).   + $0.00

TOTAL NATIONAL FEE = $860.00

Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be
accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) **(check if applicable).**   ☐ $0.00

TOTAL FEES ENCLOSED = $860.00

Amount to be: refunded	$
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☐   A check in the amount of   to cover the above fees is enclosed.

☒   Please charge my Deposit Account No.   **50-0877**   in the amount of **$860.00**   to cover the above fees.
        A duplicate copy of this sheet is enclosed.

☒   The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment
      to Deposit Account No.   **50-0877.**   A duplicate copy of this sheet is enclosed.

**NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR
1.137(a) or (b)) must be filed and granted to restore the application to pending status.**

SEND ALL CORRESPONDENCE TO:

Richard T. Knauer
Roche Diagnostics Corporation
9115 Hague Road, Bldg. D
P.O. Box 50457
Indianapolis, IN 46250-0457
Telephone No.: (317) 521-7464
Facsimile No.: (317) 521-2883

SIGNATURE

Richard T. Knauer

NAME

35,575

REGISTRATION NUMBER

28 March 2001

DATE

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

In re: patent application of	)
	)
MILTNER, Karl, et al.	) Examiner
	)
METHOD FOR THE PHOTOMETRIC	)
ANALYSIS OF TEST ELEMENTS	) Group Art Unit
	)
Serial No. 09/806,115 (PCT/EP99/07222)	)
	)
Filed: International filing date 29 September 1999	)
	)
Attorney File No. BMID9817US	)

PRELIMINARY AMENDMENT UNDER
PCT ARTICLE 28 AND 37 C.F.R. 1.121

Commissioner of Patents
U.S. Patent and Trademark Office
Washington, D.C. 20231

Sir:

Prior to the initial examination of this application by the United States Patent and Trademark Office, the applicants hereby amend the application submitted herewith as follows:

In the Specification:

The paragraph bridging pages 14 and 15 is amended to read:

Monitoring the control area enables an earlier detection of the presence of sample liquid in the control area than when measuring in the detection area. When liquid is detected a signal can be emitted which terminates supply of sample liquid. The signal can be an optical and/or an acoustic signal. In the case of a capillary gap test element this for example means that blood supply to the capillary gap can be terminated. Consequently it is possible to prevent unnecessary supply of further sample liquid and thus to reduce the required amount of sample and on the other hand this procedure shortens the time required to supply sample liquid which is convenient for the user. Nevertheless the method according to the invention still ensures that the detection area or detection areas of the detection zone are adequately supplied with sample liquid. For this purpose it is advantageous when the detection area is nearer than the control area to the first zone which firstly comes into contact with the sample liquid. Thus the test element is wetted with sample liquid in the area of the detection zone earlier than in the area of the control zone and when sample liquid is present in the area of the control zone it is ensured that the detection zone is also supplied with sample liquid. According to the invention it is also preferred that the control area (area A in figure 6) is irradiated with radiation that is absorbed by the sample liquid itself. Even if the sample liquid does not itself absorb radiation or only partially absorbs radiation there is usually a decrease in the reflected or transmitted radiation when the control zone is moistened. As a result the presence of sample liquid can already be determined before a reaction with reagents has taken place in the detection zone. Figure 7 shows that a decrease in reflection in area A of the detection zone shown in figure 6 is already found in the time interval II. This is due to the fact that a thorough moistening of the control area A can be very rapidly detected by a 880 nm light-emitting diode. Detection of a wetting of this area on the basis of a colour formed in the detection zone would not have been possible until time interval IV. In the method according to the invention in which sample application is detected, the control area is preferably on the detection zone. This not only reduces the time until detection but also allows a compact construction of such an instrument in which the optical components can be in close vicinity to one another.

- 2 -

In the Claims:

The applicants hereby restate the claims of the present application as follows:

1. (Amended)   A method for the photometric analysis of test elements having a detection zone, the method being tolerant of positioning variations of the detection zone, comprising the steps of

a) placing a test element in a holder such that the detection zone of the test element is positioned relative to an illumination unit having a first and a second light source, a positioning variation of the detection zone occurring in at least one direction,

b) contacting the detection zone with a sample such that a detection system present in the detection zone leads to a photometrically detectable change in the detection zone when an analyte is present in the sample,

c) activating the first light source to irradiate a first region of the detection zone, and detecting at least one of light reflected from the detection zone or light transmitted through the detection zone, in order to generate a first detection signal,

d) activating the second light source to irradiate a second region of the detection zone which is displaced relative to the first region in the direction of the positioning variation and detecting at least one of light reflected from the detection zone or light transmitted through the detection zone in order to generate a second detection signal,

e) comparing the first and the second detection signal and determining whether the first and/or the second detection signal has been obtained by illuminating an area situated completely on the detection zone and selecting the corresponding detection signal, and

f) determining the analyte concentration contained in the sample by analysing the selected detection signal.

2. (Amended)   A method as claimed in claim 1, wherein the detection signal that has a lower intensity is selected.

3. (Amended)   A method as claimed in claim 1, further comprising the steps of:

g)   determining a first and a second base-line detection signal on an unused test element, and

h)   standardizing the first and the second detection signal by division by the corresponding base-line detection signal before determining the analyte concentration in step f).

4. (Amended)   A method as claimed in claim 1, wherein the first region irradiated by the first light source and the second region irradiated by the second light source have essentially the same size.

5. (Amended)   A method as claimed in claim 1, wherein the test element is a capillary gap test element.

6. (Amended)   A method as claimed in claim 1, further comprising the step of: arranging the first and second light source such that focal points of the light sources are located in a connecting line running essentially parallel to the width X of the detection zone.

7. (Amended)   A method as claimed in claim 6, wherein the test element is a capillary gap test element containing a capillary gap, and the width X is arranged essentially perpendicular to the capillary gap.

8. (Amended)   A method as claimed in claim 1, wherein the regions irradiated by the first light source and by the second light source are ovals.

9. (Amended)   A method as claimed in claim 1, wherein the regions irradiated by the first light source and by the second light source are rectangles.

10. (Amended)   A method as claimed in claims 1, 8 or 9, wherein the first and second irradiated regions overlap.

- 4 -

11. (Amended)   A method as claimed in claim 10, wherein the maximum overlap is less than half the diameter of the irradiated regions.

12. (Amended)   A method as claimed in claim 6, wherein the first region has a width d1 and the second region has a width d2, and the first and second regions overlap over a maximum width "a" in the direction of the connecting line whereby the following applies:

$$d1 + d2 - a < X.$$

13. (Amended)   A method as claimed in claim 12, in which the following applies:

$$a < (d1 + d2)/2.$$

14. (Amended)   A method as claimed in claim 1, further comprising the steps of:

a) activating at least one further light source which irradiates a third region and

b) detecting a change in at least one of reflected or transmitted light from the third region to detect the presence of the sample.

15. (Amended)   A method as claimed in claim 14, wherein the at least one further light source emits radiation in a second wavelength range that is different from that of the first and second light sources and radiation in this second wavelength is detected in order to detect the presence of sample.

16. (Amended)   A method as claimed in claim 15, wherein the second wavelength range is in the range of 800 to 950 nm.

17. (Amended)   A method as claimed in claim 14, wherein the third region is located on the detection zone.

18. (Amended)   A method as claimed in claim 17, wherein the sample is brought into flow contact with the detection zone and the third region is located downstream of the first and second region.

19. (Amended)   A device for the photometric analysis of test elements comprising:

- 5 -

- an illumination unit comprising at least a first and a second light source,

- a holder for holding a test element with a detection zone in such a manner that the detection zone is positioned relative to the illumination unit,

- a control unit which activates the first light source during a first activation phase in order to illuminate a first region of the detection zone and activates the second light source during a second activation phase in order to illuminate a second region of the detection zone,

- a detection unit with at least one detector which detects light reflected from the detection zone or transmitted through the detection zone, the signal generated by the detection unit during the first activation phase being recorded as the first detection signal and the signal generated during the second activation phase being recorded as the second detection signal,

- an analytical unit which compares the first and second detection signal and determines whether the first and/or the second detection signal has been obtained by illuminating a region situated completely on the detection zone, and analyses a corresponding analyte detection signal in order to determine an analyte concentration in a sample.

20. (Amended)   A device as claimed in claim 19, wherein the illumination unit has at least one additional third light source which emits radiation in a second wavelength range that is different from the first and second light sources and radiation transmitted or reflected in this second wavelength range is detected.

21. (Amended)   A device as claimed in claim 20, wherein the second wavelength range is 800 to 950 nm.

22. (Amended)   A device as claimed in claim 20, wherein the third light source irradiates a region of the detection zone which does not overlap with the first and second regions.

23. (Amended)   A method for the photometric analysis of a test element with detection of sample application on a flat detection zone of the test element comprising the steps

- irradiating a control region of the detection zone,

- supplying sample liquid to the detection zone in such a manner that a first zone of the detection zone comes into contact with sample liquid earlier than a second zone which is laterally displaced from the first zone,

- monitoring radiation reflected from the control zone or transmitted through the control zone,

- detecting presence of the sample liquid in the control region from a change of the reflected or transmitted radiation,

- irradiating [irradiation of] at least one detection region of the detection zone, wherein the detection region is nearer to the first zone than the control region,

- detecting radiation reflected from or transmitted through the detection region,

- generating a signal that can be recognized by a user of the test element to terminate supply of sample liquid when the presence of sample liquid is detected in the control region, and

- analysing the detected radiation to determine the concentration of an analyte in the sample liquid.

24. (Amended)   A method as claimed in claim 23, wherein the test element includes a capillary gap.

25. (Amended)   A method as claimed in claim 24, wherein the capillary gap runs below the detection zone.

26. (Amended)   A method as claimed in claim 23, wherein the detection region is nearer to the first zone than the control region.

- 7 -

27. (Amended)   A method as claimed in claim 23, wherein the control region is irradiated with radiation that is absorbed by the sample liquid.

28. (Amended)   A method as claimed in claims 23 or 27, wherein the detection region is irradiated with radiation that is essentially not absorbed by sample liquid.

29. (Amended)   A method as claimed in claim 23, wherein the signal that can be recognized by a user is an optical and/or an acoustic signal.

<u>Remarks</u>

By this amendment, the applicants seek to place the present application in a form more suited to examination in the United States Patent and Trademark Office. Specifically, the applicants seek to introduce into the specification specific language supporting claim 29. This has been accomplished by introducing the underlined portion of the paragraph bridging pages 14 and 15 of the specification as reproduced below:

Monitoring the control area enables an earlier detection of the presence of sample liquid in the control area than when measuring in the detection area. When liquid is detected a signal can be emitted which terminates supply of sample liquid. <u>The signal can be an optical and/or an acoustic signal.</u> In the case of a capillary gap test element this for example means that blood supply to the capillary gap can be terminated. Consequently it is possible to prevent unnecessary supply of further sample liquid and thus to reduce the required amount of sample and on the other hand this procedure shortens the time required to supply sample liquid which is convenient for the user. Nevertheless the method according to the invention still ensures that the detection area or detection areas of the detection zone are adequately supplied with sample liquid. For this purpose it is advantageous when the detection area is nearer than the control area to the first zone which firstly comes into contact with the sample liquid. Thus the test element is wetted with sample liquid in the area of the detection zone earlier than in the area of the control zone and when sample liquid is present in the area of the control zone it is ensured that the detection zone is also supplied with sample liquid. According to the invention it is also preferred that the control area (area A in figure 6) is irradiated with radiation that is absorbed by the sample liquid itself. Even if the sample liquid does not itself absorb radiation or only partially absorbs radiation there is usually a decrease in the reflected or transmitted radiation when the control zone is moistened. As a result the presence of sample liquid can already be determined before a reaction with reagents has taken place in the detection zone. Figure 7 shows that a decrease in reflection in area A of the detection zone shown in figure 6 is already found in the time interval II. This is due to the fact that a

thorough moistening of the control area A can be very rapidly detected by a 880 nm light-emitting diode. Detection of a wetting of this area on the basis of a colour formed in the detection zone would not have been possible until time interval IV. In the method according to the invention in which sample application is detected, the control area is preferably on the detection zone. This not only reduces the time until detection but also allows a compact construction of such an instrument in which the optical components can be in close vicinity to one another.

The applicants also seek to remove any improper multiple dependency from the claims. The applicants also seek to more accurately reflect the sense of the invention through the selection of terminology and positive recitation of steps and elements, as well as through careful attention to antecedents throughout the claims. The actual changes in the claims can be seen from the following reproduction of the restated claims wherein the added text is underlined and the deleted text is bracketed.

1. (Amended)   A method [Method] for the photometric analysis of test elements having [with] a detection zone, the method being tolerant of [which is stable towards] positioning variations [tolerances] of the detection zone, comprising the steps of

   a) placing a test element in a holder such that the detection zone of the test element is positioned relative to an illumination unit having a [with at least one] first and a second light source, a positioning variation [tolerance] of the detection zone occurring in at least one direction,

   b) contacting [a sample with] the detection zone with a sample such that a detection system present in the detection zone leads to a photometrically detectable change in the detection zone when an analyte is present in the sample,

c) activating the first light source to irradiate a first region of the detection zone, and detecting <u>at least one of</u> [the] light reflected from the detection zone or <u>light</u> transmitted through the detection zone, in order to generate a first detection signal,

d) activating the second light source to irradiate a second region of the detection zone which is displaced relative to the first region in the direction of the positioning <u>variation</u> [tolerance] and detecting <u>at least one of</u> [the] light reflected from the detection zone or <u>light</u> transmitted through the detection zone in order to generate a second detection signal,

e) comparing the first and the second detection signal and determining whether the first and/or the second detection signal has been obtained by illuminating an area situated completely on the detection zone and selecting the corresponding detection signal, <u>and</u>

f) determining the analyte concentration contained in the sample by analysing the selected detection signal.

2. (Amended)   <u>A method</u> [Method] as claimed in claim 1, wherein the detection signal that has a lower intensity is selected.

3. (Amended)   <u>A method</u> [Method] as claimed in claim 1, <u>further comprising the steps of:</u>

<u>g) determining</u> [wherein appropriate steps are carried out in steps c) and d) before the detection zone is contacted with <u>the</u> sample according to step b) in order to determine] a first and a second base-line detection signal on an unused test element<u>,</u> and

<u>h)standardizing</u> [wherein] the first and the second detection signal [are standardized] by division by the corresponding base-line detection signal before determining the analyte concentration in step f).

4. (Amended)   A method [Method] as claimed in claim 1, wherein the first region irradiated by the first light source and the second region irradiated by the second light source have essentially the same size.

5. (Amended)   A method [Method] as claimed in claim 1, wherein the test element is a capillary gap test element.

6. (Amended)   A method [Method] as claimed in claim 1, further comprising the step of: arranging [wherein the detection zone has a width X and] the first and second light source [are arranged] such that focal points of the light sources are located in a connecting line [between the focal points of the regions irradiated by the light sources runs] running essentially parallel to the width X of the detection zone.

7. (Amended)   A method [Method] as claimed in claim [claims 5 and] 6, wherein the test element is a capillary gap test element containing a capillary gap, and the width X is arranged essentially perpendicular to the capillary gap.

8. (Amended)   A method [Method] as claimed in claim [claims] 1 [or 5], wherein the regions [region] irradiated by the first light source and [the region irradiated] by the second light source are ovals.

9. (Amended)   A method [Method] as claimed in claim [claims] 1 [or 5], wherein the regions [region] irradiated by the first light source and [the region irradiated] by the second light source are rectangles.

10. (Amended)   A method [Method] as claimed in claims 1, 8 or 9, wherein the first and second irradiated regions overlap.

11. (Amended)   A method [Method] as claimed in claim 10, wherein the maximum overlap is less than half the diameter of the irradiated regions.

12. (Amended)   A method [Method] as claimed in claim 6 [1], wherein the [detection zone has a width X and a connecting line between the first region and second [irradiated] region is arranged essentially parallel to the width X, the] first region [irradiated by the first light source] has a width d1 and the second region

- 12 -

[irradiated by the second light source] has a width d2, and the <u>first and second</u>
[irradiated] regions overlap over a maximum width "a" in the direction of the
connecting line whereby the following applies:

d1 + d2 - a < X.

13. (Amended)   <u>A method</u> [Method] as claimed in claim 12, in which the following
applies:

a<(d1 + d2)/2.

14. (Amended)   <u>A method</u> [Method] as claimed in claim 1, [wherein the illumination
unit has] <u>further comprising the steps of:</u>

<u>a) activating</u> at least one further light source which irradiates a third region and

<u>b)</u> detecting a change in <u>at least one of</u> [the irradiation] reflected or transmitted
<u>light</u> from the third region [is detected in order] to detect the presence of
<u>the</u> sample.

15. (Amended)   <u>A method</u> [Method] as claimed in claim 14, wherein the at least one
<u>further</u> [additional] light source emits radiation in a second wavelength range that
is different from that of the <u>first and second</u> [at least two] light sources and
radiation [transmitted or reflected] in this second wavelength is detected in order
to detect the presence of sample.

16. (Amended)   <u>A method</u> [Method] as claimed in claim 15, wherein the second
wavelength range is in the range of 800 to 950 nm.

17. (Amended)   <u>A method</u> [Method] as claimed in claim 14, wherein the third region
is located on the detection zone.

18. (Amended)   <u>A method</u> [Method] as claimed in claim 17, wherein the sample is
brought into flow contact with the detection zone and the third region is located
downstream of the first and second region.

19. (Amended)   A device [Device] for the photometric analysis of test elements comprising:

- an illumination unit comprising at least a first and a second light source,

- a holder for holding a test element with a detection zone in such a manner that the detection zone is positioned relative to the illumination unit,

- [a detection unit with at least one detector which detects light reflected from the detection zone or transmitted through the detection zone,]

- a control unit which activates the first light source during a first activation phase in order to illuminate a first region of the detection zone and activates the second light source during a second activation phase in order to illuminate a second region of the detection zone, [and]

- a detection unit with at least one detector which detects light reflected from the detection zone or transmitted through the detection zone, the signal generated by the detection unit during the first activation phase [is] being recorded as the first detection signal and the signal generated during the second activation phase [is] being recorded as the second detection signal,

- an analytical unit which compares the first and second detection signal and determines whether the first and/or the second detection signal has been obtained by illuminating a region situated completely on the detection zone, and analyses a corresponding analyte detection signal [is analysed] in order to determine an analyte concentration in a sample.

20. (Amended)   A device [Device] as claimed in claim 19, wherein the illumination unit has at least one additional third light source which emits radiation in a second wavelength range that is different from the first and second [at least two] light sources and radiation transmitted or reflected in this second wavelength range is detected.

21. (Amended)   A device [Device] as claimed in claim 20, wherein the second
    wavelength range is 800 to 950 nm.

22. (Amended)   A device [Device] as claimed in claim 20, wherein the third light
    source irradiates a region of the detection zone which does not overlap with the
    first and second regions [illuminated region].

23. (Amended)   A method [Method] for the photometric analysis of a test element
    with detection of sample application on a flat detection zone of the test element
    comprising the steps

    - irradiating a control region of the detection zone.

    - supplying sample liquid to the detection zone in such a manner that a first zone
        of the detection zone comes into contact with sample liquid earlier than a
        second zone which is laterally displaced from the first zone.

    - monitoring [the] radiation reflected from the control zone or transmitted through
        the control zone.

    - detecting presence of the sample liquid in the control region from [as a result
        of] a change of the reflected or transmitted radiation.

    - irradiating [irradiation of] at least one detection region of the detection zone,
        wherein the detection region is nearer to the first zone than the control
        region.

    - detecting radiation [which has been] reflected from [the detection region] or
        transmitted through the detection region.

    - generating a signal that can be recognized by a user of the test element to
        terminate supply of sample liquid when the presence of sample liquid is
        detected in the control region, and

    - analysing the detected radiation to determine the concentration of an analyte in
        the sample liquid.

- 15 -

[wherein

when the presence of sample liquid is detected in the control region a signal that can be recognized by the user is generated so that the supply of sample liquid can be terminated.]

24. (Amended) A method [Method] as claimed in claim 23, wherein the test element includes [is] a capillary gap [test element].

25. (Amended) A method [Method] as claimed in claim 24, wherein the capillary gap runs below the detection zone.

26. (Amended) A method [Method] as claimed in claim 23, wherein the detection region is nearer to the first zone than the control region.

27. (Amended) A method [Method] as claimed in claim 23, wherein the control region is irradiated with radiation that is absorbed by the sample liquid.

28. (Amended) A method [Method] as claimed in claims 23 or 27, wherein the detection region is irradiated with radiation that is essentially not absorbed by sample liquid.

29. (Amended) A method [Method] as claimed in claim 23, wherein the signal that can be recognized by a user is an optical and/or an acoustic signal.

Applicants submit that with the forgoing amendments, the present application satisfies all

requirements for grant of a patent, and allowance of the present application is respectfully requested.

Respectfully submitted,

A. James Richardson
Reg. No. 26,983

BRINKS HOFER GILSON & LIONE
One Indiana Square, Suite 2425
Indianapolis, Indiana 46204-2033
Telephone: (317) 636-0886
Fax: (317) 634-6701

Certificate of Mailing
Under 37 C.F.R. 1.8(a)

I hereby certify that this correspondence is being deposited with the United States Postal Service as First Class Mail, Postage Prepaid, in an envelope addressed to: Assistant Commissioner of Patents, U.S. Patent and Trademark Office, Washington, D.C. 20231, dated August 31, 2001.

A. James Richardson
Registration No. 26,983

Method for the photometric analysis of test elements

The invention concerns a method for the photometric analysis of test elements with detection zones, said method being stable in relation to positioning tolerances of the detection zone.

The photometric analysis of test elements is one of the most common methods for rapidly determining the concentration of analytes in samples. Photometric analyses are generally carried out in the field of analytics, environmental analytics and above all in the field of medical diagnostics. Test elements that are analysed photometrically play an important role especially in the field of blood glucose diagnostics from capillary blood.

The general trend in performing analytical tests is to reduce the amounts of sample. This is often due to the fact that only small amounts of sample are present. For example in the field of blood sugar determination, the diabetic himself removes a drop of blood from the finger pad and a reduction in the amount of blood required for the test considerably increases the convenience. This is primarily due to the fact that it is possible to select a smaller depth of cut for the blood collection. A reduction in the amounts of sample is linked to a miniaturization of the test elements and in particular of the detection zones in which the actual reaction of the sample with the analyte takes place. Hence in order to carry out an exact photometric analysis it is

necessary to precisely position the detection zone.
Numerous test element holders are known in the prior art
which allow a quite accurate relative positioning of the
detection zone and measurement optics. The European
Patent EP-B-0 618 443 (corresponding to US-5,424,035) is
mentioned here as an example in which the detection
zones of the test element are positioned laterally as
well as vertically relative to the measurement optics.
The document EP-A-0 319 922 is also mentioned as
representative of many other analytical systems which
carry out a positioning of test strips. However, the
systems known in the prior art operate with detection
zones which exceed 5 mm x 5 mm. Consequently a
positioning in the manner known in the prior art is
relatively unproblematic. However, if the lateral
dimensions of the detection zone are reduced, great
efforts have to be made in the manufacture of the test
elements as well as in the positioning within an
analytical system in order to obtain reliable analytical
results. The object of the present invention was to
propose a method and a device for the photometric
analysis of test elements which also allow the reliable
analysis of test elements with small detection zones.

This object is achieved by a method for the photometric
analysis of test elements in which the test element is
placed in a holder in which its detection zone is
positioned such that it is disposed relative to an
illumination unit with at least two light sources. After
the detection zone has been contacted with the sample to
be analysed, a first light source is activated in order
to irradiate the detection zone. Light reflected from
the detection zone or transmitted through the detection
zone is detected as a first detection signal. Afterwards
a second light source is activated which irradiates a

second area of the detection zone which is offset from
the first area in the direction of the expected
positioning tolerance. The light reflected from this
area or transmitted through this area is detected as the
second detection signal. The detection signals obtained
from the two areas are compared and examined to
determine which of the signals was obtained by
illumination of an area situated completely in the
detection zone. A corresponding detection signal is
selected and analysed to determine the analyte
concentration in a basically known manner.

A further subject matter of the present invention is a
method which can rapidly detect whether an adequate
amount of sample liquid has been added to the test
element or the detection zone and reports this back to
the operator.

In the field of analysis with test elements it is a
considerable gain in convenience when the time required
to apply sample liquid to a test element can be reduced
and when there is also a feedback about whether the
applied amount of sample is sufficient. In the case of
test elements which utilize an electrochemical
principle, it has been common practice for some time to
indicate to the user when sample liquid has penetrated
into the analytical zone so that he can stop adding
sample. In the case of test elements based on
electrochemistry this detection can be achieved in a
simple manner by a conductivity measurement. However, in
the field of optical measurement of test elements such a
rapid application detection cannot easily be
accomplished. Methods are for example described in the
documents US-4,109,261 and EP-A-0 256 806 in which a
sample application is detected by the optical system

which carries out the measurement and is used as a start
signal for awaiting an incubation period. However, in
these described methods the user receives no feedback
about whether he has applied sufficient sample liquid
and can stop further addition. Furthermore optical
systems are used in the described methods which detect
colour formation in the detection zone of the test
element. As shown in figure 7 of this application,
several seconds pass between contacting the detection
zone with sample liquid and the start of colour
formation. If for example in the case of a blood sugar
test the user has to hold his finger on the test element
until a colour reaction is initiated this would be felt
by him to be a constraint on his personal freedom. There
is therefore a need to reduce the time for the addition
or until the detection of the sample liquid. A blood
sugar measuring instrument is described for example in
EP-A-0 166 876 in which sample application is detected
but it does not allow a check of whether the sample
quantity is adequate.

Hence a method is proposed as part of the present
invention which allows a rapid detection of sample
application on a test element. The method according to
the invention for the photometric analysis of test
elements comprises the following steps:

-   irradiation of a control area of the detection zone,

-   transporting sample liquid to the detection zone in
    such a manner that a first zone of the detection
    zone comes into contact with the sample liquid earlier
    than a second zone which is at a lateral distance from
    the first zone

- monitoring the radiation reflected from the control
  area or transmitted through the control area,

- detecting presence of sample liquid in the control
  area as a result of a change of the reflected or
  transmitted radiation

- irradiating a detection area of the detection zone

- detecting irradiation which has been reflected from
  the detection area or transmitted through the
  detection area

- analysing the detected radiation in order to
  determine the concentration of an analyte in the
  sample liquid,

  characterized in that

- when the presence of sample liquid is detected in
  the control area, a signal is emitted so that the
  supply of sample liquid can be terminated.

In the following the method according to the invention
for compensating positioning tolerances is described
first.

A device with which the method according to the
invention can be carried out has a holder in which a
test element is positioned relative to an illumination
unit which is also part of the device. Holders that are
known in the prior art and especially the holder
described in EP-B-0 618 443 can be used in the following

invention. Despite the inventive procedure which
stabilizes the analysis in relation to positioning
tolerances, it is desirable that the holder already
results in a positioning of the detection zone that is
as accurate as possible. However, the positioning
tolerances cannot be reduced below a certain threshold
which becomes clearer when one considers the individual
factors that impact on the positioning tolerances. The
analytical system already results in a number of
tolerances for a relative positioning of the holder and
illumination unit. Further tolerances are caused by the
positioning of the test element within the holder since
a certain clearance between the test element and holder
is necessary so that the user can insert the test
element in the holder. Furthermore the test element
itself is subject to certain manufacturing tolerances
which relate in particular to the width of the test
element. Finally tolerances also occur with respect to
the position of the detection zone relative to the test
element and the carrier material of the test element.
Especially in capillary gap test elements the detection
zone may be considerably displaced in the direction of
the width of the test element which is described below
in more detail.

The device according to the invention for photometric
analysis additionally comprises an illumination unit
with at least a first and a second light source. These
light sources are used to illuminate adjacent areas of
the detection zone. The light sources are arranged such
that the centres of the illuminated areas on the
detection zone are displaced relative to one another in
the direction of an expected positioning tolerance. This
can for example be achieved in that the light sources
themselves are displaced relative to one another and

radiate essentially perpendicularly onto the detection
zone. However, the light sources can also be arranged
such that they obliquely irradiate the detection zone
and the distance between the irradiated areas is
essentially achieved by the slant of the light sources
relative to the perpendicular relative to the detection
zone. In principle the light sources known in the prior
art for diagnostic detection systems are suitable as
light sources. Light-emitting diodes are preferred as
these have a relatively low energy consumption and yield
a relatively narrow band spectrum. Miniaturized light-
emitting diodes which can be mounted on a semiconductor
circuit board are particularly preferred. Such light-
emitting diodes are obtainable in sizes which result in
light spots of a suitable size on the detection zone
without interposing an optical system. However, in the
framework of the present invention it is preferable to
use an optical system comprising lenses and optionally
apertures in addition to the light sources. It is
advantageous to adapt the shape of the irradiated areas
to the shape of the detection zone and to the expected
tolerances. In the case of a rectangular detection zone
it is for example advantageous to illuminate oval areas
or even rectangular areas. This can for example be
achieved by suitable lenses or apertures.

The present invention also envisages using more than two
light sources. If a particularly large positioning
tolerance is expected in one direction of the detection
zone, it is possible for example to use three light
sources which illuminate areas on the detection zone
which are displaced in the direction of the expected
positioning tolerance. The present invention is also
suitable for reducing the impact of positioning
tolerances in more than one direction. For example four

light sources can be used which illuminate four areas
that are arranged in the shape of a square or rectangle.
Such an arrangement can prevent measurement errors due
to positioning inaccuracies in the direction of the one
side of the square as well as in the perpendicular
direction.

In a method for photometric analysis of test elements a
sample is contacted with the detection zone of the test
element. The contacting is understood either as a direct
application of the samples on the detection zone or a
transport of the sample into the detection zone. The
latter is in particular the case for capillary gap test
elements in which the sample (usually capillary blood
from the finger pad) is guided to the capillary gap and
is transported through this into the detection zone.
Embodiments are also conceivable in which a solid sample
is applied to a fleece by for example rubbing a fleece
on an object and the sample is subsequently transported
by means of an auxiliary fluid from the fleece to the
detection zone as is for example the case in some rapid
drug tests. In addition there are chromatographic test
strips in which the sample is transported into the
detection zone by means of absorbent materials. Hence
the aforementioned shows that samples within the sense
of the invention are primarily sample liquids such as
blood but solid sample materials can also be used.

Sample that has been brought into contact with the
detection zone leads to a detectable change of the
detection zone in test elements. The generation of
detectable changes as a result of a reaction of an
analyte contained in the sample with a reagent system is
well-known in the prior art and thus does not have to be
further elucidated here. However, it is relevant for the

present invention that the detectable change can be adequately detected with the light sources and detector that are used. This is the case when a colour is formed in the detection zone which absorbs the radiation emitted by the light sources and thus attenuates the transmitted or reflected light. However, the converse case is also possible in which a dye whose presence is detected photometrically is destroyed by the reaction of the reagent system with an analyte and the actual measured signal is a decrease in the attenuation of the transmitted or reflected light. The term light or light source should be understood in the scope of the invention to encompass wavelength ranges that can be used by optical arrangements i.e. UV and IR in addition to the visual range.

The well-known detectors in the prior art and especially semiconductor detectors can be used for the present invention. It is important to select the detector or detectors such that the radiation reflected from the detection zone or transmitted through the detection zone leads to a signal when the detector is illuminated with this radiation. Detectors which have their sensitivity maximum in the range of the reflected or transmitted radiation can be used advantageously. Optionally it is also possible to use filters which allow the measurement radiation to pass selectively in order to make the detection more stable towards the effects of interfering light.

In order to carry out the method according to the invention a first light source of the illumination unit is firstly activated to irradiate a first area of the detection zone and the signal present at the detector during the activation is recorded as a first detection

signal. Subsequently the first light source is
deactivated and the second light source is activated to
irradiate a second area and the signal present at the
detector is recorded as the second detection signal.
Electric circuits and methods for activating light
sources, especially light-emitting diodes are
sufficiently well-known in the prior art. Reference is
made by way of example to the document US-5,463,467 in
which an activation of light-emitting diodes is
described for carrying out photometric analyses. The
present invention also envisages activating light
sources by means of signals which enable the influence
of foreign light to be eliminated from the detected
signal as described for example in the said document
US-5,463,467.

An important step in the method according to the
invention is to compare the detected signals and
determine which of the signals or whether both signals
have been obtained by illumination of an area which lies
completely on the detection zone. This determination can
be carried out in various ways. If the analyte results
in a colour forming reaction in the detection zone, the
first and second detection signal can be compared and
the light signal that has been more greatly attenuated
is selected as lying completely on the detection zone.
If in contrast a reaction is carried out in which colour
is degraded by the analyte, the signal which has been
subjected to the least attenuation is selected as the
one which is located completely on the detection zone.
These two procedures can be carried out without having
to carry out a measurement on the detection zone before
reaction with the analyte in order to determine a blank
value. However, according to the invention it is
preferred that first measurements are carried out on the

detection zone with a first and second light source before carrying out the reaction with the sample. The detection signals determined in this manner can be used as a basis for determining which signal results from an irradiated area that is located completely within the detection zone and as a base value (so-called blank value) for determining the analyte concentration. If measurements have been carried out with the light sources on a test element that has not yet reacted, then the inventive determination step can be advantageously carried out by determining the signal amplitude before and after reaction of the detection zone with the sample and selecting that light source for the determination of the analyte concentration which yielded the larger signal amplitude.

The selection of at least one of the two light sources as suitable for determining the analyte concentration can also be carried out without having to contact the detection zone with the sample. This can for example be achieved when the detection zone is composed of a light material and the test element has a dark colour in the area bordering the detection zone. If measurements are carried out on such a test element with a first and second light source and the measurements are compared, the light source from which the higher reflectance signal was obtained can be selected as being suitable for determining the analyte concentration. It is additionally possible to make the detection zone at least partially transparent whereas the area of the test element bordering the detection zone is essentially impermeable to light. If a transmission measurement is now carried out, the light source can be selected with which a higher transmission was obtained. If reference was made above to a higher or lower signal, this can

mean a "crude signal" which is present at the detector
when the light sources are activated. The crude signals
are advantageously corrected before comparing them i.e.
the illumination geometry and the variation of intensity
from light source to light source are taken into
account. This can for example be achieved by
standardizing the signals on the basis of blank values
(forming a ratio between the actual signal and the
signal for an unreacted test element or standard).

The present invention additionally concerns a method for
the photometric analysis of a test element in which
sample application is detected. In this method as so-
called control area of the detection zone of a test
element is firstly irradiated and the radiation
reflected from this control area or transmitted through
the control area is monitored. In this connection
monitoring means that the reflected or transmitted
radiation is measured at intervals. Usually measurements
are carried out at intervals of fractions of a second.
The time intervals are selected in practice such that
the time interval between two measurements is less than
the time delay which can be tolerated for the detection
of a change in the measured value. During the monitoring
of the control area, a sample liquid is supplied to the
detection zone and this is carried out in such a manner
that a first zone of the detection zone comes into
contact with the sample liquid earlier than a second
zone which is laterally spaced from the first zone. In
this connection the term lateral refers to the plane of
the detection zone. Hence there is a spacing between the
first and the second zone when the detection zone is
observed from the upper side. Such a transport of sample
liquid to a detection zone occurs for example in
chromatographic test strips in which the sample or a

reaction solution of the sample penetrates from one side
into the detection zone and laterally migrates through
the detection zone. Such a supply of sample liquid also
occurs when a capillary gap test element is used in
which the capillary gap and detection zone are disposed
in the same plane. This can for example be achieved in
such a manner that the capillary gap ends at an edge of
the detection zone and sample liquid from the capillary
gap penetrates from this site of contact into the
detection zone or the capillary gap can be located below
the detection zone as shown in figure 1. In the said
cases the sample liquid comes into contact with the
first zone of the detection zone earlier than with a
second zone. In figure 6 this is indicated by the zones
Z1 and Z2. The sample liquid penetrates via a capillary
gap which is located below the detection zone (10) into
the detection zone in the direction of the arrow. In
this case the zone Z1 comes into contact with the sample
liquid earlier than zone Z2.

In the method according to the invention a sample
application is detected on the basis of a change in the
reflected or transmitted radiation in the control area.
In this connection a change means that a signal change
occurs during the monitoring i.e. the transmission or
reflection signals obtained from the unreacted control
area of the detection zone are different from those
obtained from a control area which is moistened
thoroughly with sample liquid or which has reacted with
sample liquid.

In order to analyse the test element, at least one
detection area of the detection zone is irradiated and
the radiation that is reflected from this area or
transmitted through the detection area is detected and

analysed in order to determine the concentration of an
analyte in the sample liquid. Details on the detection
and analysis have already been described above for an
inventive method for compensating positioning
tolerances.

Monitoring the control area enables an earlier detection
of the presence of sample liquid in the control area
than when measuring in the detection area. When liquid
is detected a signal can be emitted which terminates
supply of sample liquid. In the case of a capillary gap
test element this for example means that blood supply to
the capillary gap can be terminated. Consequently it is
possible to prevent unnecessary supply of further sample
liquid and thus to reduce the required amount of sample
and on the other hand this procedure shortens the time
required to supply sample liquid which is convenient for
the user. Nevertheless the method according to the
invention still ensures that the detection area or
detection areas of the detection zone are adequately
supplied with sample liquid. For this purpose it is
advantageous when the detection area is nearer than the
control area to the first zone which firstly comes into
contact with the sample liquid. Thus the test element is
wetted with sample liquid in the area of the detection
zone earlier than in the area of the control zone and
when sample liquid is present in the area of the control
zone it is ensured that the detection zone is also
supplied with sample liquid. According to the invention
it is also preferred that the control area (area A in
figure 6) is irradiated with radiation that is absorbed
by the sample liquid itself. Even if the sample liquid
does not itself absorb radiation or only partially
absorbs radiation there is usually a decrease in the
reflected or transmitted radiation when the control zone

is moistened. As a result the presence of sample liquid
can already be determined before a reaction with
reagents has taken place in the detection zone. Figure 7
shows that a decrease in reflection in area A of the
detection zone shown in figure 6 is already found in the
time interval II. This is due to the fact that a
thorough moistening of the control area A can be very
rapidly detected by a 880 nm light-emitting diode.
Detection of a wetting of this area on the basis of a
colour formed in the detection zone would not have been
possible until time interval IV. In the method according
to the invention in which sample application is
detected, the control area is preferably on the
detection zone. This not only reduces the time until
detection but also allows a compact construction of such
an instrument in which the optical components can be in
close vicinity to one another.

The present invention is elucidated in more detail in
the following on the basis of some figures:

Figure 1:   Perspective and cross-sectional representation
            of a capillary gap test element

Figure 2:   Cross-section through a device lengthwise to
            an inserted test element

Figure 3:   Cross-section through a device at right angles
            to the test element

Figure 4:   Block diagram of an analytical device

Figure 5:   Position of irradiated areas on the detection
            zone

Figure 6:   Irradiated areas on the detection zone

Figure 7:   Signal time course measured in the control area

Figure 8:   Signal time course when the test element is
            displaced.

Figure 1A shows a perspective view of a capillary gap
test element. The test element has a carrier foil (2)
and a cover foil (3). A spacer (4) which has a recess is
located between these foils to form a capillary gap
between the carrier foil and cover foil. In order to
carry out a diagnostic test, sample liquid which is
usually capillary blood is brought to the opening (5) of
the capillary gap. The sample liquid is moved through
the channel due to capillary forces and reaches the
reagent paper (6). The reagent paper (6) is in turn also
mounted on a spacer (4) so that only the middle part of
the reagent paper is wetted with sample when sample
liquid is present in the capillary gap (7) and only this
part forms a colour or generates a signal. This middle
region that can be used to determine the analyte
concentration is referred to as the detection zone (10).
In the example shown the detection zone has a size of
ca. 2 x 3 mm. Such a small detection zone gives rise to
two particular problems concerning the measurement. On
the one hand the signal obtained from the detection zone
must be of adequate strength to allow a reliable
determination of the analyte concentration and, on the
other hand, it must be ensured that when analysing the
detection zone there are no contributions from
reflectance from outside the detection zone. In practice
both requirements are closely linked since in order to
increase the measurement signal one will try to measure

the detection zone as completely as possible which,
however, means that there is a risk of obtaining
contributions from outside the detection zone if one
cannot guarantee an exact positioning of the detection
zone relative to the illumination unit. The problem of
positioning is particularly pronounced in capillary gap
test elements since there is a relatively large
variation in the position of the capillary gap as a
result of the manufacturing process. However, the
present invention enables in a simple manner, on the one
hand, analysis of a relatively large part of the
detection zone and, on the other hand, avoidance of
erroneous contributions from regions outside the
detection zone.

Figure 2 shows a cross-sectional view of a device
according to the invention (20) lengthwise to a test
element (1). The device (20) has a channel in which a
test element (1) can be inserted. Figure 2 shows the
positioning of a test element in an analytical position.
The device has a movably mounted pin (21) with a
downwards tapering conical end to hold the test element
in this position when the positioning is suitable, the
tip of the pin is located in a recess of the test
element such that the test element is fixed and
positioned in the direction of its longitudinal axis.
The pin (21) can also be used to electrically signal the
presence of a test element or its positioning. For this
purpose the pin is designed to be electrically
conductive and a contact (26) is provided on the
opposing side of the device. When a test element is not
present, the pin is pressed against the contact (26) by
a spring which makes an electrical contact between these
two elements. If a test element is now inserted, it
slides firstly between the pin (21) and contact (26) and

thus breaks the electrical contact. However, when it is slided further, the pin (21) engages through the groove of the test element and the electrical contact closes again.

Figure 2 shows another optical arrangement for analysing the test element. In the analytical position the detection zone (10) of the test element is positioned relative to a lens (22) on the opposite side of which light sources (23, 24) are located. The light source (23) is used to illuminate the detection zone in order to determine an analyte concentration. Light source (24) illuminates a zone on the detection zone which is at a greater distance from the application opening (5) for the sample liquid than the zone illuminated by the light source (23). Hence the light source (24) can be used to carry out the method according to the invention for detecting sample application. Due to the required degree of miniaturization the light sources (23, 24) are in the form of light-emitting diodes which are directly mounted on the semiconductor circuit board.

Figure 2 also shows a semiconductor detector (25) which detects radiation reflected from the detection zone.

The lateral positioning of the test element in the device is shown in figure 3. The test element (1) is located in a channel (30) which prevents lateral movement as far as possible. As a result of the manufacturing tolerances of the test elements, the dimensions of the channel (30) must be such that it can also receive the largest expected test elements. This means that due to manufacture, it is not possible to ideally position smaller test elements in the channel

(30) and lateral movement is possible. The method
according to the invention can be used to nevertheless
reliably measure a signal of the detection zone for all
test elements which originates from an illuminated
region which is completely on the detection zone. For
this purpose the device has the light sources (23, 23')
which are arranged next to one another in a direction
perpendicular to the test element. It is advantageous
for the optical arrangement when the light sources are
focused on the detection zone of the test element by
means of a lens (22) or a lens system. The distance
between the light sources and between the light sources
and detection zone and the design of the lens (22) is
selected such that the boundary conditions elucidated
below in connection with figure 5 are met.

Figure 4 shows a schematic block diagram of a device for
the photometric analysis of test elements. The first
light source L1 and the second light source L2 are
arranged next to one another such that they illuminate
different but overlapping regions B1 and B2 on the
detection zone (10). The detector (D) receives the
diffusely reflected radiation from the detection zone
(10) and passes the corresponding signal to the control
unit (S). The control unit successively activates the
light sources L1 and L2 and registers each of the
signals received by the detector. These signals are
passed onto the evaluation unit (A) where the signals
are compared and a suitable signal is selected as
described above. In the example shown both regions B1
and B2 are completely on the detection zone (10) and
thus both can be used to calculate the analyte
concentration. Hence one of the signals is used to
calculate an analyte concentration in a known manner
which is then passed onto the display (DIS). In the

present case an averaged signal can also be used to
determine the concentration.

Figure 5 shows some examples of how the irradiated
regions can be arranged relative to one another and
relative to the detection zone. Figure 5A shows a
particularly preferred embodiment in which the
illuminated regions B1 and B2 have an oval shape and
partially overlap. In the example shown the signal
detected from the illuminated region B2 is used to
calculate the analyte concentration since this region is
located completely on the detection zone (10) whereas a
signal obtained from the region B1 is falsified due to
contributions from outside the detection zone. Figure 5A
additionally shows a coordinate system which is intended
to simplify the description of the figures. The
arrangement of illuminated regions selected in figure 5A
is intended to compensate a positioning tolerance of the
detection zone in the direction of the X axis. In this
case the illuminated regions are selected such that a
connecting line through their focal points is
essentially parallel to the direction in which a
positioning tolerance is expected or to be compensated.
Figure 5B shows an embodiment which enables the
positioning tolerance to be compensated in the direction
of the X axis as well as of the Y axis. In this case
four illuminated regions have been selected which are
displaced relative to one another in the direction of
the X and the Y axis. Since the regions B1, B3 and B4
result in reflectances with components from outside the
analytical zone, the region B2 is used for the analysis
since this is completely within the detection zone.

Figure 5C shows an embodiment which can compensate for
particularly large variations in the position of the

detection zone in the direction of the X axis. Three
illumination regions that are spaced apart have been
selected in the direction of the X axis in which the
positioning tolerance is critical. If only regions B1
and B2 would have been used, a suitable analysis would
not have been possible, but this is now possible by
means of region B3.

Figure 5D shows a less preferred embodiment in which the
illuminated regions B1 and B2 do not overlap and there
is even a clear region between them. As shown in the
figure positions can occur with this arrangement in
which an exact analysis is not possible with either of
the illuminated regions. Hence within the scope of the
present invention it is preferred that the illuminated
regions overlap or at least are directly adjacent to one
another.

Figure 5E also shows a less preferred embodiment. In
this case the illuminated regions are selected to be so
large that both extend beyond the detection zone when
the detection zone is positioned centrally. The
detection zone cannot be exactly analysed with either of
the two regions. Hence within the scope of the present
invention it is preferred that the total width (b) of
the two light sources is smaller than the corresponding
width of the detection zone. Hence the size of each
individual illuminated region must be smaller than that
of the detection zone. As already mentioned the aim
should be to make the illuminated regions as large as
possible in order to obtain a maximum signal yield and
thus a good signal/noise ratio. In the individual case a
compromise must be reached between the size of the
illuminated regions and their overlap which on the one
hand ensures that always one of the illuminated regions

is completely on the detection zone with the expected positioning tolerances and, on the other hand, that the signal obtained from an individual illuminated region is large enough to ensure the required accuracy of the analysis.

Figure 5F shows a diagram that can be used to determine the maximum allowable positioning tolerance for a given arrangement. Two illuminated regions B1 and B2 are shown which each have a width (d) in the direction of the positioning tolerance. The illuminated regions B1 and B2 overlap in the direction of the positioning tolerance by the distance "a" so that the overall width "b" is 2d - a. In the limiting position P1 is still completely on the detection zone whereas the opposite limiting position P2 (dashed) the region B1 is still just completely on the detection zone. Hence the maximum variation in positioning that can be tolerated by the arrangement is X - a in which X is the width of the detection zone in the direction of the positioning tolerance. If the width X of the detection zone is known and also the maximum shift of position that can occur from one extreme position into the other (T_{max}) then it is possible to calculate the required overlap "a" of the illuminated regions as X - T_{max}.

As already mentioned the width b; (b = 2 d - a) should be smaller than X in order to avoid the case shown in figure 5 E. If this is generalized for different diameters (d1, d2) it follows that d1 + d2 - a < X. If the required overlap has been accordingly selected with regard to the expected positioning tolerance, then this allows the maximum diameter d (or the width in the case of regions that are not round) of an individual illuminated region to be calculated as follows: d = (X + a)/2. The maximum

overlap of the regions should be preferably selected such that it is smaller than half the diameter of the width $(a < (d1 + d2)/2)$. As a rule it is not only the linear overlap "a" that is important for a suitable selection of the overlap, but also the ratio of the size of the overlapping area ($F_{ü}$) to the area of an irradiated region (F_B). It turned out experimentally that $F_{ü}/F_B$ is advantageously less than 0.3 and particularly advantageously between 0.2 and 0.1.

The above-mentioned geometric considerations should not obscure the fact that experiments are usually necessary to determine the optimal relationships. This is partly due to the fact that the illuminated regions shown only partly describe the true conditions. Usually it can be assumed that it is reasonable to make the calculations on the basis of regions that represent about 90 % of the total intensity. However, this means that a certain proportion of reflected radiation already comes from outside the detection zone if the marked illuminated region is at the border. Furthermore a problem in practice is that there are manufacturing variations in the adjustment of the light sources and thus tolerances in the overlap of the illuminated regions also have to be taken into account. Hence in practice one would preferably design a device according to the invention such that in an extreme position at least one of the light sources completely irradiates the detection zone and is at a distance of ca. 10 % of the light spot diameter from the nearest edge of the detection zone.

Figure 6 shows a detection zone and the irradiated regions B1, B2 and region A. The arrow in figure 6 shows the direction of flow of sample liquid in a capillary gap test element according to figure 1. Accordingly the

liquid firstly comes into contact with the detection
zone below the regions B1 and B2 and subsequently with
zone A. The position of region A is advantageously
selected such that it is not overlapped or only partly
overlapped by the regions B1 and B2. Whereas regions B1
and B2 are preferably analysed in a wavelength range
which is absorbed by the colour formed in the detection
zone but not by the sample as such, a wavelength is
preferably used to measure region A in which the sample
itself absorbs. In the case of aqueous liquids infrared
radiation which is in the range of the water bands can
for example be used to analyse region A. However, it is
preferable to use a wavelength in the range of 800 to
950 nm which can be used to detect an absorption of the
intrinsic colour of blood. After applying sample liquid
to a capillary gap test element according to figure 1,
region A is continuously measured and the radiation
transmitted through the detection zone or reflected from
the detection zone is detected. This can be achieved
with the same detector that is also used for the
subsequent analysis of regions B1 and B2. However, it is
preferable to use a special detector that is adapted to
the irradiation range used for region A.

Figure 7 shows the signal time course obtained from the
analysis of region A. At time 0 blood fluid is applied
to the capillary gap. During the time interval I no
significant reduction in reflectance is measured in
region A for all curves. A reduction in reflectance is
found in range II for the curves K1, K2 and K3 (glucose
concentration: K1:25 mg/dl; K2:250 mg/dl; K3:500 mg/dl)
which were recorded with capillary blood. The decrease
in reflectance shows that the sample liquid has arrived.
The instrument can now indicate to the user that he can
stop adding the sample liquid since sufficient liquid is

present to carry out the analytical test. The advantage
for the user is that he can use smaller amounts of blood
and the time required for the application can be
shortened. A continuous decrease in reflectance is seen
in range IV in figure 7 which is due to the formation of
colour in the detection zone. This shows that an
indication of sufficient sample being present based on
colour formation in the detection zone would not have
been possible until seconds later since the colour
formation requires a certain time. The gain in time of 3
to 4 seconds already represents a considerable gain in
comfort for the user.

Figure 7 in addition shows the curve K4 which was
obtained from a colourless glucose solution and
detection at 880 nm. In contrast to the curves K1, K2
and K3, this curve shows no significant decrease in
reflectance in the time ranges II and III, but only in
range IV when colour formation begins. Hence on the
basis of the time course of the signal detected in
region A of the detection zone it is possible to
differentiate between sample liquid, in particular
blood, and a glucose solution used as a control or to
calibrate the instrument. If the instrument recognizes
that a control solution has been used then it can carry
out a measurement and calibrate itself. In this case a
correction factor can for example be used which is
calculated from the ratio between the measured
concentration and the true concentration of the control
solution. Subsequent measured values can then be
automatically corrected by the instrument by dividing by
the correction factor. The true concentration of the
control solution can for example be stored in the
instrument especially when only one set control solution
is used or the concentration can be entered into the

instrument by the user.

Figure 8 shows two signal curves measured at the detector (25; fig. 2) for different positions of the test element. The relative position of the test element in millimeters is shown on the abscissa of the figure.

The position of the test element (1) shown in figure 3 in which the capillary gap (5) is located centrally above the lens (22) represents the zero position. Positive values of the abscissa represent a lateral displacement of the test element at right angles to the capillary gap. Hence figure 8 shows how the measured signal behaves when the test element is not positioned centrally or/and the capillary gap is not arranged centrally on the test element as a result of the manufacturing.

The signals measured at the detector are shown in arbitrary units on the ordinate. Diffusely reflected radiation is detected by the test element as a result of the selected measuring geometry shown in figures 2 and 3.

The signal curves shown in figure 8 show that the signals are highest near to the zero position. This is due to the fact that the measurements were carried out on a white reagent paper (6) without sample application. The reflectance is highest before sample application in the region of the reagent paper below which the capillary gap is located and which is used as the actual measurement region after sample application.

The reflectances are somewhat lower outside this region although reflectance is still obtained from the reagent

paper. This is due to the fact that a coloured foil has been glued to the back of the reagent paper in these regions.

Curve 50 which is composed of measurement points that are shown as squares, shows the signal curve when the light source (23) is activated. In contrast curve 60 which is composed of measurement points that are shown as rhombi shows the signal curve when the test element is displaced when the light source (23') is activated.

Figure 8 shows that in the range of ca. 0 to + 1 mm it is possible to carry out a measurement with light source (23) and a measurement with light source (23') in the range of ca. -1 to 0 mm. Hence the arrangement can tolerate a positioning tolerance of $\pm$ 1 mm.

Claims

1. Method for the photometric analysis of test
   elements with a detection zone which is stable
   towards positioning tolerances of the detection
   zone comprising the steps

   a) placing a test element in a holder such that the
       detection zone of the test element is positioned
       relative to an illumination unit with at least
       one first and a second light source, a
       positioning tolerance of the detection zone
       occurring in at least one direction,

   b) contacting a sample with the detection zone such
       that a detection system present in the detection
       zone leads to a photometrically detectable change
       in the detection zone when an analyte is present
       in the sample,

   c) activating the first light source to irradiate a
       first region of the detection zone and detecting
       the light reflected from the detection zone or
       transmitted through the detection zone in order
       to generate a first detection signal,

   d) activating the second light source to irradiate a
       second region of the detection zone which is
       displaced relative to the first region in the
       direction of the positioning tolerance and
       detecting the light reflected from the detection
       zone or transmitted through the detection zone in

order to generate a second detection signal,

e) comparing the first and the second detection signal and determining whether the first and/or the second detection signal has been obtained by illuminating an area situated completely on the detection zone and selecting the corresponding detection signal,

f) determining the analyte concentration contained in the sample by analysing the selected detection signal.

2. Method as claimed in claim 1, wherein the detection signal that has a lower intensity is selected.

3. Method as claimed in claim 1, wherein appropriate steps are carried out in steps c) and d) before the detection zone is contacted with sample according to step b) in order to determine a first and a second base-line detection signal on an unused test element and wherein the first and the second detection signal are standardized by division by the corresponding base-line detection signal before determining the analyte concentration in step f).

4. Method as claimed in claim 1, wherein the first region irradiated by the first light source and the second region irradiated by the second light source have essentially the same size.

5. Method as claimed in claim 1, wherein the test element is a capillary gap test element.

6. Method as claimed in claim 1, wherein the detection
    zone has a width X and the first and second light
    source are arranged such that a connecting line
    between the focal points of the regions irradiated
    by the light sources runs essentially parallel to
    the width.

7. Method as claimed in claims 5 and 6, wherein the
    width is arranged essentially perpendicular to the
    capillary gap.

8. Method as claimed in claims 1 or 5, wherein the
    region irradiated by the first light source and the
    region irradiated by the second light source are
    ovals.

9. Method as claimed in claims 1 or 5, wherein the
    region irradiated by the first light source and the
    region irradiated by the second light source are
    rectangles.

10. Method as claimed in claims 1, 8 or 9, wherein the
    first and second irradiated regions overlap.

11. Method as claimed in claim 10, wherein the maximum
    overlap is less than half the diameter of the
    irradiated regions.

12. Method as claimed in claim 1, wherein the detection
    zone has a width X and a connecting line between
    the first and second irradiated region is arranged
    essentially parallel to the width, the region
    irradiated by the first light source has a width d1

and the region irradiated by the second light
source has a width d2 and the irradiated regions
overlap over a maximum width "a" in the direction
of the connecting line whereby the following
applies:

d1 + d2 - a < X.

13. Method as claimed in claim 12, in which the
following applies:

a<(d1 + d2)/2.

14. Method as claimed in claim 1, wherein the
illumination unit has at least one further light
source which irradiates a third region and a change
in the irradiation reflected or transmitted from
the third region is detected in order to detect the
presence of sample.

15. Method as claimed in claim 14, wherein the at least
one additional light source emits radiation in a
second wavelength range that is different from that
of the at least two light sources and radiation
transmitted or reflected in this second wavelength
is detected in order to detect the presence of
sample.

16. Method as claimed in claim 15, wherein the second
wavelength range is in the range of 800 to 950 nm.

17. Method as claimed in claim 14, wherein the third
region is located on the detection zone.

18. Method as claimed in claim 17, wherein the sample is brought into flow contact with the detection zone and the third region is located downstream of the first and second region.

19. Device for the photometric analysis of test elements comprising:

    - an illumination unit comprising at least a first and a second light source,

    - a holder for holding a test element with a detection zone in such a manner that the detection zone is positioned relative to the illumination unit,

    - a detection unit with at least one detector which detects light reflected from the detection zone or transmitted through the detection zone,

    - a control unit which activates the first light source during a first activation phase in order to illuminate a first region of the detection zone and activates the second light source during a second activation phase in order to illuminate a second region of the detection zone and the signal generated by the detection unit during the first activation phase is recorded as the first detection signal and the signal generated during the second activation phase is recorded as the second detection signal,

- an analytical unit which compares the first and second detection signal and determines whether the first and/or the second detection signal has been obtained by illuminating a region situated completely on the detection zone and a corresponding detection signal is analysed in order to determine the analyte concentration in the sample.

20. Device as claimed in claim 19, wherein the illumination unit has at least one additional third light source which emits radiation in a second wavelength range that is different from the at least two light sources and radiation transmitted or reflected in this second wavelength range is detected.

21. Device as claimed in claim 19, wherein the second wavelength range is 800 to 950 nm.

22. Device as claimed in claim 19, wherein the third light source irradiates a region of the detection zone which does not overlap with the first and second illuminated region.

23. Method for the photometric analysis of a test element with detection of sample application on a flat detection zone of the test element comprising the steps

    - irradiating a control region of the detection zone

- supplying sample liquid to the detection zone in such a manner that a first zone of the detection zone comes into contact with sample liquid earlier than a second zone which is laterally displaced from the first zone

- monitoring the radiation reflected from the control zone or transmitted through the control zone

- detecting presence of sample liquid in the control region as a result of a change of the reflected or transmitted radiation

- irradiation of at least one detection region of the detection zone

- detecting radiation which has been reflected from the detection region or transmitted through the detection region

- analysing the detected radiation to determine the concentration of an analyte in the sample liquid

wherein

a signal is generated when the presence of sample liquid is detected in the control region so that the supply of sample liquid can be terminated.

24. Method as claimed in claim 23, wherein the test element is a capillary gap test element.

25. Method as claimed in claim 24, wherein the capillary gap runs below the detection zone.

26. Method as claimed in claim 23, wherein the detection region is nearer to the first zone than the control region.

27. Method as claimed in claim 23, wherein the control region is irradiated with radiation that is absorbed by the sample liquid.

28. Method as claimed in claims 23 or 27, wherein the detection region is irradiated with radiation that is essentially not absorbed by sample liquid.

29. Method as claimed in claim 23, wherein the signal is an optical and/or an acoustic signal.

Abstract

The invention concerns a method for the photometric
analysis of test elements with a detection zone which is
stable towards positioning tolerances of the detection
zone comprising the following steps: activating the
first light source to irradiate a first region of the
detection zone and detecting the light reflected from
the detection zone or transmitted through the detection
zone in order to generate a first detection signal (50),
activating the second light source to irradiate a second
region of the detection zone which is displaced relative
to the first region in the direction of the positioning
tolerance and detecting the light reflected from the
detection zone or transmitted through the detection zone
in order to generate a second detection signal (60),
comparing the first and the second detection signal and
determining whether the first and/or the second
detection signal has been obtained by illuminating an
area situated completely on the detection zone. The
invention also concerns a device to carry out this
method and a method for the photometric analysis of a
test element with detection of sample application.
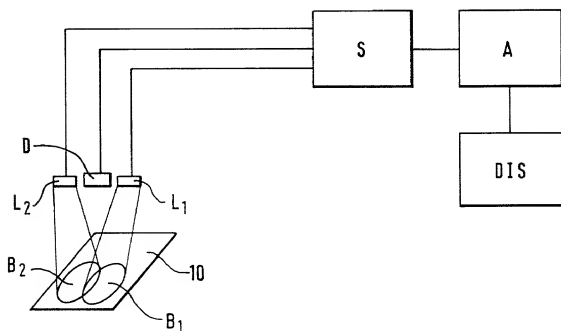
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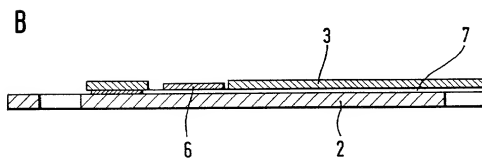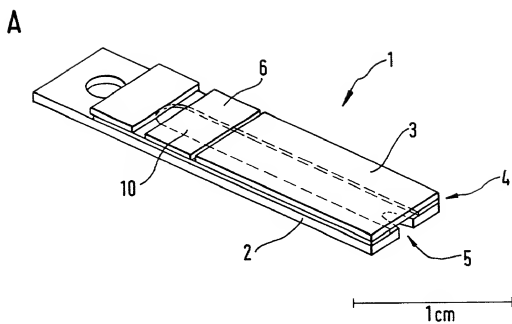
A

1cm

B

Fig. 2
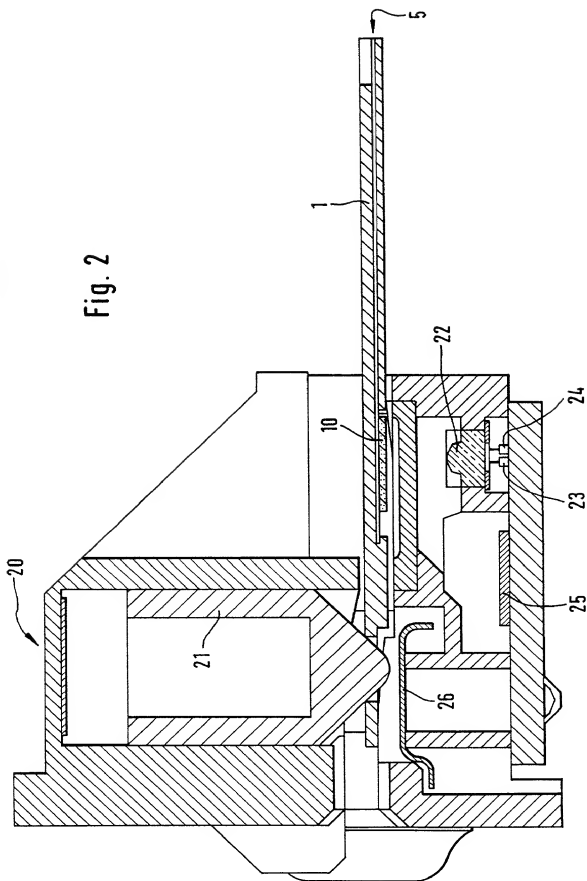
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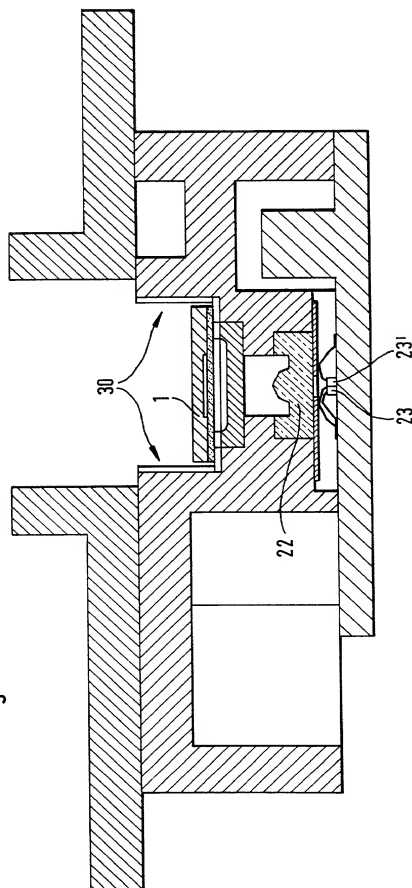
Fig. 4

Fig. 5

09/806115
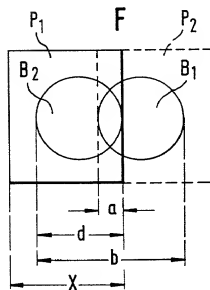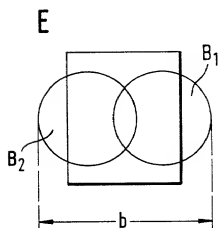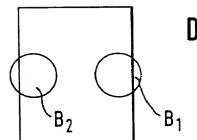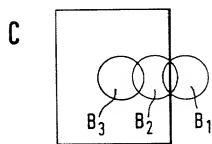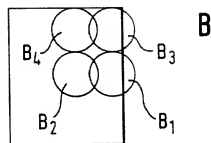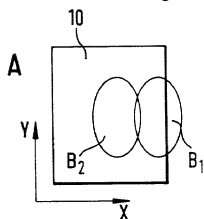
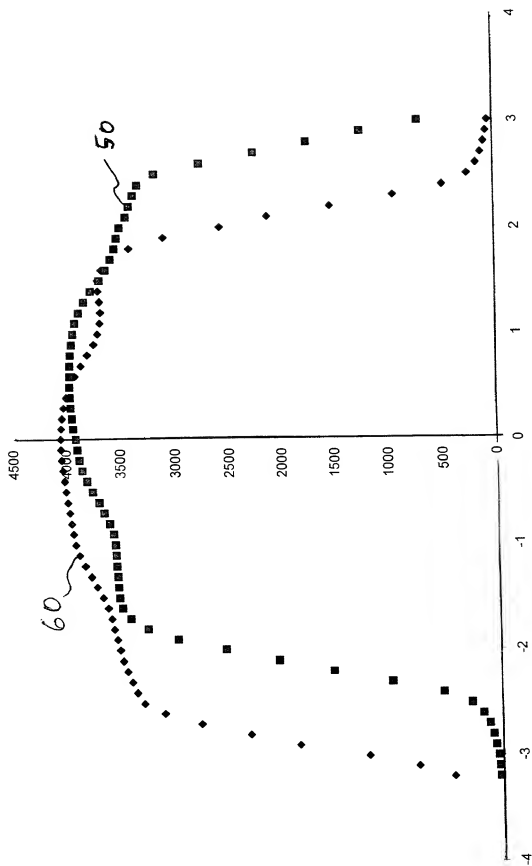Fig. 6
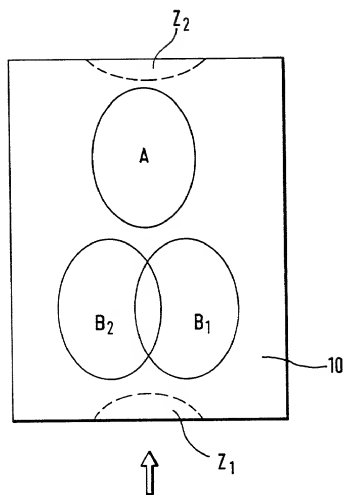
Fig. 7
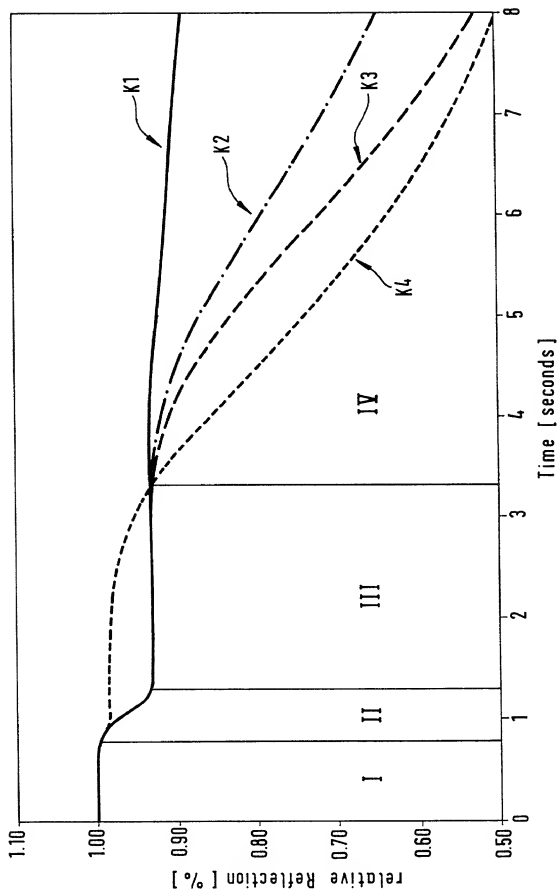
Fig 8

Docket No.
BMID9817US

Declaration and Power of Attorney For Patent Application

English Language Declaration

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

METHOD FOR THE PHOTOMETRIC ANALYSIS OF TEST ELEMENTS

the specification of which

(check one)

☐ is attached hereto.

☒ was filed on   **March 28, 2001**_____ as United States Application No. or PCT International Application Number **09/806,115**_____

and was amended on _____
<div align="center">(if applicable)</div>

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)   Priority Not Claimed

198 44 500.8	Germany	29 September 1998	☐
(Number)	(Country)	(Day/Month/Year Filed)	
PCT/EP99/07222	PCT	29 September 1999	☐
(Number)	(Country)	(Day/Month/Year Filed)	
			☐
(Number)	(Country)	(Day/Month/Year Filed)	

I hereby claim the benefit under 35 U.S.C. Section 119(e) of any United States provisional application(s) listed below:

_____   _____
(Application Serial No.)   (Filing Date)

_____   _____
(Application Serial No.)   (Filing Date)

_____   _____
(Application Serial No.)   (Filing Date)

I hereby claim the benefit under 35 U. S. C. Section 120 of any United States application(s), or Section 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. Section 112, I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, C. F. R., Section 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application:

_____   _____   _____
(Application Serial No.)   (Filing Date)   (Status)
                                                          (patented, pending, abandoned)

_____   _____   _____
(Application Serial No.)   (Filing Date)   (Status)
                                                          (patented, pending, abandoned)

_____   _____   _____
(Application Serial No.)   (Filing Date)   (Status)
                                                          (patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. *(list name and registration number)*

Richard T. Knauer, Reg. No. 35,575
D. Michael Young, Reg. No. 33,819
Brent A. Harris, Reg. No. 39,215
Kenneth J. Waite, Reg. No. 45,189
Marilyn L. Amick, Reg. No. 30,444
Michelle Neff, Reg. No. 47,817
Jill L. Woodburn, Reg. No. 39,874

Send Correspondence to: Richard T. Knauer
Roche Diagnostics Corporation
9115 Hague Road, Bldg. D, P.O. Box 50457
Indianapolis, IN 46250-0457

Direct Telephone Calls to: *(name and telephone number)*
Richard T. Knauer, Telephone No. (317) 521-7464

Full name of sole or first inventor
MILTNER, Karl

Sole or first inventor's signature	Date
Karl Miltner	22-5. 2001

Residence
Ernst-Ludwig-Kirchner-Strasse 22, D-67227 Frankenthal, Germany DEX

Citizenship
German

Post Office Address
(same as residence address)

Full name of second inventor, if any
RUPPENDER, Uwe

Second inventor's signature	Date
Uwe Ruppender	22.07.2001

Residence
Ifflandstrasse 7, D-68161 Mannheim, Germany DEX

Citizenship
German

Post Office Address
(same as residence)

Full name of third inventor, if any
WERSIG, Christian

Third inventor's signature _Clstian Wers Christian Wers_ ✓ Date **20.07.2001**

Residence
Feuerbergstrasse 7, D-67134 Birkenheide, Germany *DEX*

Citizenship
German

Post Office Address
(same as residence)

Full name of fourth inventor, if any
ZIMMER, Volker

Fourth inventor's signature _Voller Zim_ ✓ Date **28.05.2001**

Residence
Wilhelmstrasse 64, D-69221 Dossenheim, Germany *DEX*

Citizenship
German

Post Office Address
(same as residence)

Full name of fifth inventor, if any

Fifth inventor's signature   Date

Residence

Citizenship

Post Office Address

Full name of sixth inventor, if any

Sixth inventor's signature   Date

Residence

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09/806115

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Application

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Assistant Commissioner for Patents
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Application Number	09/806,115
Filing Date	March 28, 2001
First Named Inventor	Karl MILTNER et al.
Group Art Unit	Not Yet Assigned
Examiner Name	Not Yet Assigned
Attorney Docket Number	9793/081

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[ ]   Assignee of record of the entire interest.
       Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96).

[XX]   Attorney or Agent of record.

[ ]   Registered practitioner named in the application transmittal letter in an application without an executed oath or declaration. See 37 CFR 1.33(a)(1). Registration Number _____

Typed or Printed Name	A. James Richardson, Reg. No. 26,983
Signature	
Date	8/31/01

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

[XX] *Total of ____1____ forms are submitted.